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Dated: July 16, 2007 Signature: (Christine Willis)

Docket No.: 0020-4348P
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Eijiro WATANABE et al.

Application No.: 08/992,914 Confirmation No.: 4405

Filed: December 18, 1997 Art Unit: 1638

For: RAFFINOSE SYNTHASE GENES AND THEIR USE Examiner: D. H. Kruse

REPLY BRIEF

MS Reply Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant submits herewith a Reply Brief in triplicate as required by 37 C.F.R. § 1.192. This Brief on Appeal responds to the Examiner's Answer dated June 30, 2005.

For clarity, the issues presented in the Appeal Brief filed April 8, 2005, will be repeated, and the Reply to the Examiner's Answer will correspond structurally to the arguments section in the Appeal Brief.

This brief contains items under the following headings as required by 37 C.F.R. § 41.41 and M.P.E.P. § 1208:

I. STATUS OF CLAIMS
II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL
III. ARGUMENT
IV. CONCLUSION
V. UPDATE OF RELATED APPEALS

I. STATUS OF CLAIMS

The following is the status of the claims as of the mailing of the Examiner's Answer on May 16, 2007:

Claims 6, 43 and 46-86 are pending in the application.

Claims 6 and 43 are allowed. The Examiner's decision rejecting claims 46-86 has been appealed.

Claims 46-51 stand rejected under 35 U.S.C. § 101.

Claims 52-74, 77 and 82-86 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support in the specification.

Claims 46-86 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement by the disclosure of the specification.

Claims 46, 47, 52, 53, 55 and 59-86 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-**3**, 16-23 and 28-30 of copending application no. 09/301,766. Appellants wish to reiterate that they will address this rejection in either this or the copending application upon a finding in one application or the other that claims are allowed.

Compared to the status of the claims at the filing of the Appeal Brief, the rejection of claims 46-51, 75 and 76 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description support by the specification, has been withdrawn. Also, the basis for the provisional obviousness-type double patenting rejection over copending application no. 09/301,766 has been changed to include claim 3 of the copending application.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are to be reviewed on appeal:

Claims 46-51 are rejected under 35 U.S.C. § 101, for alleged lack of support by either a substantial asserted utility or by a well-established utility. (As stated in paragraph 4 of the Final Office Action.)

Claims 48-77 and 82-86 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description of the claimed invention. (As stated in paragraph 5 of the Final Office Action.)

Claims 52-74, 77 and 82-86 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable an isolated nucleic acid of SEQ ID NO: 4, 6 or 8, nor an isolated nucleic acid isolated from any leguminous, lamiaceous or monocotyledonous plant. (As stated in paragraph 6 of the Final Office Action.)

III. ARGUMENT

A. Rejection under 35 U.S.C. § 101

The Examiner presents two new arguments is support of his rejection of claims 46-51 under 35 U.S.C. § 101. The first is based upon newly introduced evidence, in the form of the Osumi patent 6,891,084 (identified as "NEW" at page 3 of the Examiner's Answer) and more particularly the alignment of SEQ ID NO: 24 from the Osumi '084 patent against SEQ ID NO: 4 of the present application.

Appellants in the first instance request that the Examiner's new evidence be excluded from consideration. It is improper to introduce new evidence into the record once prosecution has closed, unless such evidence is relevant to a **new** ground of rejection. 37 C.F.R. 41.33(2). Furthermore, the Examiner's new evidence is introduced without any explanation at all of how it was created, for example the Examiner's reasons for believing that SEQ ID NO: 24 of Osumi '084 actually encodes a raffinose synthase enzyme. Appellants, and the Board, are thus left with little basis for actually understanding the true weight of the evidence. Accordingly, all of the Examiner's arguments that rely upon the newly introduced evidence of the Osumi patent and the alignment of sequences newly presented with the Examiner's Answer should be struck from the record.[1]

[1] The arguments to be struck are at page 6, line 12 to page 7, line 6; page 11, line 20 to page 12, line 6 and page 26, lines 9 to 16.

The following text is from the file history of Osumi '084, and relates to the identity of SEQ ID NO: 24. The Examiner states at page 5 of the Office Action dated September 20, 2001 (emphasis added):

> 9. Claims 7-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.
>
> The nucleic acid of instant application was isolated in the following manner: Primers based on a cDNA (SEQ ID NO: 4) encoding a raffinose synthase from cucumber were used to amplify a partial raffinose synthase gene from Arabidopsis (pg 65, lines 5-23). The Arabidopsis gene was used as a probe to isolate SEQ ID NO: 23 (which encodes SEQ ID NO: 24) from soybean (pp 66, lines 13-31). The cucumber DNA could not be used directly as a probe for isolation of the gene from soybean (pg 63, lines 5-26). The protein encoded by SEQ ID NO: 23 has only 37.6% homology to the raffinose synthase encoded by SEQ ID NO: 4.
>
> A sequence search detected two proteins with much greater similarity to the protein of SEQ ID NO: 24. Fujikur et al.(1995, GenBank Accession No. S45033) teach a protein with 76.5% homology and Heck et al (1993 GenBank Accession No. S27762) teach one with 71.1% homology. Both of these proteins are thought to be associated with seed imbibition. Another piece of information that suggests that SEQ ID NO: 23 does not encode a raffinose synthase comes from Table 3 of the instant application, where it shows that plants transformed with a vector comprising SEQ ID NO: 23 had raffinose contents no different from wild-type plants.
>
> The instant application fails to teach a specific utility for a gene encoding a protein involved in seed imbibition.

Notwithstanding the procedural issue that requires exclusion of the evidence of the Osumi '084 patent, the Board should take note **of the Examiner's conclusion** that the SEQ ID NO: 24 of Osumi '084 appears to be the amino acid sequence of a Seed Imbibition Protein ("SIP"), not of a raffinose synthase enzyme, **based upon the high degree of homology of SEQ ID NO: 24 to a SIP**. The USPTO should not be permitted to adopt opposite views on the reliability of an assertion of enzyme activity based upon sequence identity as the circumstances suit the Office. That is, Examiners should not be permitted to argue that a high degree of sequence identity supports a rejection based upon an asserted enzyme activity different from that urged by an Applicant on one hand, then on the other argue that an Applicant is not entitled to urge that a high degree of sequence identity supports an assertion of a particular enzyme activity when an Applicant relies upon this for an asserted utility.

Osumi responded to the Office Action by submitting their Amendment & Request for Reconsideration dated March 20, 2002 (copy attached), proffering the following remarks:

The Examiner has alleged that specification fails to set forth a specific asserted utility and, as such, one of the skill in the art would not know how to use the claimed invention. Further, based on this position, the Examiner has asserted that the skilled artisan could not use the invention.

In support of this position, the Examiner has stated that the data presented in Table 3 demonstrates the plants transformed with a vector comprising SEQ ID NO; 23 yielded raffinose content that were not different from wild-type plants (pages 4-5 of the Official Action). However, the Examiner has mischaracterized the data in Table 3 for at least the following reasons, and therefore these two grounds of rejections are believed to be unsustainable.

Table 3 is reproduced below.

Table 3

Plant	Raffinose content (mg/g)
Wild type	0.20
Transformant (pSleRSI)	0.00
Transformant (pBIcRS9)	0.00
Transformant (pl3lsRSl)	0.22

The full-length cucumber cDNA was isolated and described as SEQ ID NO: 4 on page 62, lines 8-10. An Arabidopsis thaliana cDNA was obtained by PCR resulting in the sequence SEQ ID NO: 27 (see page 65, lines 15-20). The Arabidopsis thaliana cDNA was used to obtain a soybean cDNA encoding raffinose synthase and is shown in SEQ ID NO: 23, which is in the vector pMOSSloxSRS (see page 67, lines 15-20). In Example 5 on page 68, line 18 to page 69, line 4, the Applicants described the construction of plasmids pBIcRS1 and pBIcRS9, which are derived from the cDNA obtained in Example 3 (see page 68, lines 18-20: cucumber cDNA: SEQ ID NO:4), which are present in the reverse orientation thereby providing antisense RNA. The results in Table 3 show that when these anti-sense constructs were expressed in the plants, the raffinose content decreased (comparing the raffinose in wild-type of 0.20 mg/g to the raffinose content in the two transformants: 0.00).

The plasmid pBIsRS1 was constructed from the soybean cDNA (see page 69, lines 5-30, where the raffinose synthase obtained from pMOSSloxSRS (SEQ ID NO:23) was used). As shown in Table 3, when this plasmid was transformed into a plant, a notable increase in raffinose was observed (compare 0.20 in wild-type to 0.22 in the transformant).

Therefore, a clear and specific utility is not only set forth in the present application but is supported by data. Withdrawal of this ground of rejection is requested."

Then, in the Office Action dated July 1, 2002 (page 3), the rejection based on lack of utility was withdrawn (emphasis added):

> 8. The rejection of claims 7-17 under 35 U.S.C, 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility is WITHDRAWN in light of Applicant's arguments filed 20 March, 2002, that urge that the data in Table 3 of the instant specification shows that plants transformed with anti-sense constructs have reduced raffinose content.

The Board should note first that the plasmid introduced into plants transformed with anti-sense constructs having reduced raffinose content shown in Table 3 is **not** that constructed from the soybean cDNA (SEQ ID NO: 23). Rather, it is the cucumber cDNA (SEQ ID NO: 4), which is the nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 5 in the Nagasawa Declarations.

SEQ ID NO: 4 of the present application has 75% sequence identity of SEQ ID NO: 2 of the present application whose raffinose synthase activity has been confirmed. Thus, the antisense knockout experiment of Osumi provides results consistent with Appellants' assertion that high sequence identity to a known raffinose synthase (RFS) is indicative that an amino acid sequence actually encodes a RFS.

Third, in view of the very low degree of sequence identity to an enzyme shown by antisense knockout to encode a RFS (i.e. SEQ ID NO: 4 of Osumi '084; and subsequently, that is by the Nagasawa Declaration of the instant record, by high sequence identity to a protein demonstrated biochemically to encode a RFS), the Board should be careful about drawing a firm conclusion about the identity of SEQ ID NO: 23 as a RFS. It is true that a plant transformed with SEQ ID NO: 23 shows a small increase (about 10%) in raffinose content, and this certainly provides a possibility that SEQ ID NO: 23 does encode a RFS. However, there is no demonstration that this is actually due to increased RFS activity. That is, the increase in raffinose content might be due to increased activity of a different enzyme in the raffinose biosynthetic pathway, e.g. enzymes in the pathway that produce substrate for RFS and thus drive a higher amount of raffinose biosynthesis.

The Board should consider that it is not false-negative results that are of concern here, but only false-positive results. That is, the possibility that the sequence identity analysis by which the artisan identifies an enzyme as a RFS might mistakenly omit an enzyme from that class is not relevant to the

issue of utility. Rather, it is the situation that the analysis mistakenly includes embodiments that are not operable that is at issue. Therefore, even if SEQ ID NO: 23 of Osumi '084 does in fact encode a RFS, the failure of sequence identity analysis as urged by Appellants to properly identify it as a RFS does not harm the argument that such analysis is sufficient to establish utility of an enzyme, since utility as a RFS would only be ascribed to those enzymes that do show high sequence identity to a RFS.

The Examiner also argues that "Appellant[s'] assertion is based on facts that were not know[n] until after the filing of the instant Application." See, page 9, lines 18-19 of the Examiner's Answer. This is incorrect. Appellants' assertion of utility of enzymes encoded by nucleic acids cloned according to the teachings of the present specification, due to their activity as RFSs is made based on facts known at the time of filing of the application. That is, the facts relied upon in making the original assertion of utility are either presented in the specification itself, or were known in the art. Such facts include: 1) the cloning of DNA encoding an enzyme established by biochemical experiment to be a RFS; 2) the successful cloning, by use of primers having sequences found in common with another RFS-encoding nucleic acid, of additional nucleic acids encoding proteins having high similarity to the amino acid sequence of a protein shown biochemically to be a RFS; and 3) the common use in the art at the time the invention was made of sequence identity analysis to create hypotheses about the biochemical nature of proteins. The further data from additional sequences used in Dr. Nagasawa's Declaration do help strengthen the allegation of utility, in that plainly a larger database of sequences for use in analysis will improve the quality of the result. However, Appellants' initial assertion of utility is made based upon facts available at the time of filing of the application, as explained above. Furthermore, even if only the three sequences noted by the Examiner as contemporaneous with the filing of the application, those from cucumber from SEQ ID NO: 2 and SEQ ID NO: 4 are used, the Board should note that these two sequences are much more closely related to each other than to any stachyose synthase or seed imbibition protein, and so the conclusion that one can tell a RFS from a STS from a SIP based upon a degree of sequence identity remains valid. This is furthermore consistent with the expectations of one of ordinary skill in the art, since this approach to identifying biochemical function of a newly sequenced protein was common in the art at the time the invention was made as evidenced, e.g. by the use of the same approach by Richmond (2000), cited by the Examiner.

Finally, Appellants wish to simply address the statement at page 10, lines 14-15 that, "The Examiner's argument is based on the fact that it appears that only one of Appellants' amino acid sequences is actually a raffinose synthase ... ." The "fact" alleged is a conclusion reached by the

Examiner, not a fact at all. The facts are that Appellants prove by biochemical tests that one amino acid sequence (SEQ ID NO: 2) is a RFS. Additional sequences are asserted to encode RFS enzymes based upon an analysis of sequence data showing that their amino acid sequences match those of known RFSs better than they match the sequence of any other enzyme.

B. Rejection under 35 U.S.C. § 112, first paragraph, for alleged lack of written description

Claims 48-77 and 82-86 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description of the claimed invention.

The Examiner first argues *In re Wallach,* asserting that an instance in which only 5% of the amino acid sequence of a protein, which was being cloned and characterized as to sequence for the first time and about which almost nothing from the prior art was known (a protein inhibiting the cytotoxic effects of TNF), is a fact situation analogous to that of the present application, which is directed to cloned DNA encoding proteins well characterized in the prior art as to both purification and biochemistry. Furthermore, in *Wallach*, only a single example of the protein encoded by the claimed DNA (or claimed in the parent application) was provided, and no structural information beyond the first few amino acids was disclosed. In stark contrast, in the present application, four instances of isolation of cDNAs of the invention are demonstrated in working examples, and the protein encoded is one about which a great deal is known from the prior art. For instance, as disclosed in the present specification, a number of plants that express a raffinose synthase are set forth, and a set of PCR primers that effectively hybridize to the mRNA of encoding the enzyme and that can be used to isolate the cDNA encoding the message, are set forth. The disclosure of the present application is sufficiently detailed that distinct sets of primers for use in different genera of plants are provided. Furthermore, two full-length protein sequences are disclosed in the present application. The facts of *Wallach*, and those of the present application, are plainly so very different that *Wallach* is inapposite to the present appeal.

The Board should take due note of the state of the art at the time the invention was made, which included significant understanding of the biochemistry of raffinose synthase and its distribution among plants, these being significant in that one of ordinary skill in the art could easily find a source from which to isolate a nucleic acid of the invention and perform any testing

necessary to determine operability of the embodiment. *See, Capon v. Eshhar* 76 USPQ2d 1078 (Fed. Cir. 2005) and *Faulner v. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006).

The Examiner also newly argues a theory that, "one skilled in the art would have required evidence of specific function for a putative raffinose synthase because of the similarity to both stachyose synthases and seed imbibition proteins." Appellants are not sure what to make of this. Appellants note that molecular biologists routinely rely upon sequence similarity analysis to assign putative biological activities to unknown proteins. Also, the specification describes how to test any particular isolated protein, e.g. one expressed from cloned DNA according to the invention, for biochemical activity of a RFS.

Related to the rejection of claims 53-58, the Examiner also attempts to argue that, due to the very large number of species of plants falling within the families named in the claims (see, p. 16 of the Examiner's Answer). To this Appellants must simply reply, "so what?" The claimed subject matter is described in product-by-process terms, and the Examiner cannot reasonably argue that the process steps recited in the claims are not well-described in the present specification. Efficacy of the described process in obtaining nucleic acids encoding RFS enzymes is unequivocally demonstrated in four working examples from four different species in three genera. Furthermore, these claims specifically recite that the nucleic acid obtained by the process must encode a functional RFS enzyme. Thus, to the degree that some applications of the describe process might fail in some instances, those instances are excluded from the claims.

The legal test for sufficiency of written description support for a claimed invention is whether or not the specification evidences that the inventors had "possession" of the claimed invention. *Vas-Cath v. Marhurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991). Demonstrating that a described process works to obtain its intended result four times must surely evidence possession of that process, and so possession of products of that process as presently claimed.

The Examiner also asserts that "no specific sequences are claimed" in claims 53-58. This is incorrect. As explained previously, the specific sequences recited in the claims are incorporated into the product of the recited process. Those sequences are obtained from portions of the RFS gene the inventors have identified as conserved across the relevant family, and so

likely to be a structure related to the biochemical function of the enzyme. In any event, those sequences serve to distinguish the claimed subject matter from all other nucleic acids.

The Examiner also urges that *University of California v. Eli Lilly and Co.* requires sustaining of the written description rejection of claims 52-74, 77 and 82-86 for failure of the specification to provide adequate written description. The Examiner argues that, since a claim directed to a product claimed *per se*, which was written in purely functional terms (encoding a mammalian insulin), was rejected over description only of a process for obtaining the product, the present claims must also be rejected.

University of California v. Eli Lilly and Co. is not applicable to the present claims 52-74, 77 and 82-86. These claims are product-by-process claims, and include limitations as to how the product is made. The case law is quite clear that if a composition can be described in terms of how it is made, it is acceptable to make a claim in which the product is so described. *Fier v. Revel*, 25 USPQ2d 1601 (Fed. Cir. 1993).

Finally, Appellants wish to reiterate that it appears that adequacy of the written description of aspects of claims 79-81 and 83-85 that are related to plasmid and construct ("chimeric gene") components, and methods for metabolic transformation, other than as to the RFS encoding sequence have not been subject to argument by the Examiner, and therefore these are deemed acceptably supported by the specification. See, e.g. page 19, lines 1-3 of the Examiner's Answer.

C. Rejection under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement

Claims 46-77 and 78-86 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner is arguing that the breadth of the claims, beyond SEQ ID NO: 2, which has actually been demonstrated by biochemical assay to encode a RFS enzyme, is not enabled.

The Examiner newly argues at page 20, lines 15-18, that he has addressed, "by the nature of the rejection, the breadth of the claims, the nature of the invention, and the state of the prior art, and additionally addressed the predictability of the art at the time of the invention." Among

these, the nature of the rejection is irrelevant. Furthermore, glaringly absent is any discussion of the teachings of the instant specification. Even if, *arguendo*, all of these items have been addressed[2], the Examiner still has failed to address all of the factors that are to be considered under the guidance of *In re Wands*. Therefore, as Appellants have argued, the Examiner has failed to make a proper *prima facie* case for lack of enablement, and the instant rejection cannot be sustained.

Also, at page 23, lines 7-9 of the Examiner's Answer, the Examiner states, "The Examiner has provided evidence that one of skill in the art would require more than sequence similarity as evidence of function, contrary to Appellant[s'] assertion." This is not correct. The Examiner has made this requirement. As Appellants have previously shown, e.g. by the paper of Richmond (2000), the artisan of ordinary skill is willing to consider evidence from sequence comparison as at least suggestive of biological function. The required burden of persuasion is the "preponderance of the evidence." Appellants submit that an artisan of ordinary skill would accept that an enzyme that is more similar in sequence to a RFS than to a STS or SIP is more likely than not to believe that the enzyme is a STS. That is all that is legally required for enablement of the present invention.

IV. CONCLUSION

Appellants respectfully submit that the present specification provides adequate written description and enablement of the invention set forth in claims 46-86. The favorable actions of reversal of the Examiner's decisions that:

46-51 are rejected under 35 U.S.C. § 101, for alleged lack of support by either a substantial asserted utility or by a well-established utility;

Claims 48-77 and 82-86 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description of the claimed invention; and

Claims 52-74, 77 and 82-86 are rejected under 35 U.S.C. § 112, first paragraph, because the specification fails to provide enabling disclosure.

[2] Appellants do not concede this.

V. UPDATE OF RELATED APPEALS

Appellants wish to advise the Board that a Notice of Appeal was filed on December 22, 2006 in the copending application no. 09/301,766 and the Appeal Brief is expected to be filed on or before July 22, 2007.

For all of the reasons set forth above, each of the rejections in the Examiner's Answer dated June 30, 2005, is improper. It is therefore respectfully requested that the Examiner be reversed on all grounds.

Appellants have requested oral hearing at the time of filing of this Reply Brief. Appellants' Representative is available at any time to address any questions or concerns of the Board by telephone at 858-792-8855 if necessary.

Dated: July 16, 2007

Respectfully submitted,

By 

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